Stem Cell Research (2009) 3, 96–105

available at www.sciencedirect.com

www.elsevier.com/locate/scr

REGULAR ARTICLE

Governing stem cell banks and registries: Emerging Issues

Rosario M. Isasi*, Bartha M. Knoppers

Centre de Recherche en Droit Public, Faculty of Law, Université de Montréal, C.P. 6128 succ. Centre-ville, Montréal, QC, Canada H3C 3J7

Received 14 October 2008; received in revised form 30 April 2009; accepted 21 May 2009

Abstract The expansion of national and international research efforts in stem cell research is increasingly paired with the trend of establishing stem cell banks and registries. In jurisdictions crossing the spectrum of restrictive to liberal stem cell policies, banks and registries are emerging as an essential resource for transnational access to quality-controlled and ethically sourced stem cell lines. In this study, we report the preliminary findings of a survey of stem cell banks participating in the International Stem Cell Forum's International Stem Cell Banking Initiative (ISCBI). The questionnaire circulated to all ISCBI members addressed both general issues surrounding research policies (e.g., national policies regulating the permissibility of conducting embryonic stem cell research (hESCR)) and, more specifically, issues relating to the governance of stem cell banking projects. The results of the questionnaire were complemented by scholarly research conducted by the authors. This article provides an overview of the current international hESC banking landscape (I). For this purpose, the policy and governance approaches adopted in the surveyed stem cell banks at the national level will be analyzed and areas of convergence and variance will be identified (II). It is beyond the scope of this paper to provide a comprehensive analysis of the wide range of possible governance approaches, policy responses, and their implications. However, we want to provide a starting point for discussion surrounding key questions and challenges as concerns provenance, access, and deposit of hESC lines (III). Finally, while our analysis is focused on research grade hESCs, the lessons to be gleaned from this examination will encourage further thought, analysis, and research into the issues raised in the banking and governance of other sources of stem cell lines (e.g., SCNT, parthenogenesis, iPs) (IV).

Introduction

The expansion of national and international research efforts in stem cell research is increasingly paired with the trend of establishing stem cell banks and registries (e.g., UK Stem Cell Bank, USA-NIH registry, Spanish National Stem Cell Bank, European hESC registry, UMASS International Stem Cell Registry, etc.). In jurisdictions crossing the spectrum of restrictive to liberal stem cell policies (Isasi and Knoppers, 2006a), banks and registries are emerging as an essential resource for transnational access to quality-controlled and ethically sourced stem cell lines from different origins (e.g., embryonic, adult, SCNT) and grades (e.g., research, clinical).

Both stem cell banks and registries have distinct and complementary scientific value. Whereas stem cell banks represent a collection of biological materials (i.e., stem cell lines of embryonic and/or adult origin) and the associated data stored within an organized system (OECD, 2006) (e.g., UK Stem Cell Bank, Spanish Stem Cell Bank), registries consist of databases or catalogs documenting the scientific and ethical provenance of the stem cell lines (e.g., European Human Embryonic Stem Cell Registry). It is important to

* Corresponding author.
E-mail address: rosario.isasi@umontreal.ca (R.M. Isasi).

1873-5061/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.scr.2009.05.003

highlight that the term "stem cell bank" can refer to a number of different levels and types of operations as well as institutions (Stacey, 2007). Stem cell banks range from public (e.g., UK Stem Cell Bank, Spanish National Stem Cell Bank) to institutional (Tel Aviv Sourasky Medical Center Cell Bank) and commercial banks (e.g., WiCell International Stem Cell Bank), or to local laboratories (e.g., Stem Cell Research Center, Kyoto University; France Biomedicine Agency, National Registry of hESC). Moreover, the term could also refer to a centralized institute that provides cell stocks for research (US National Stem Cell Bank, Singapore Stem Cell Bank), a national supply centre, or a repository of hES cells for a broad range of researchers (e.g., Indian National Centre for Stem Cell Science,). Finally, the term "stem cell bank" could also refer to an international stem cell registry (e.g., UMass International Stem Cell Registry, European hESC Registry). Here, we will use the term "bank" to encompass all of the wide ranges of institutions referred to above.

In order to maintain internal consistency with policy frameworks relating to the permissibility of conducting stem cell research, stem cell banks and registries aim to avoid redundancy in research projects and to eliminate the need for the derivation of additional stem cell lines. The latter is of particular relevance to cell lines of embryonic origin given the surrounding political and moral controversies. Illustrative of this is the stated mandate of the United Kingdom's Stem Cell Bank "to reduce the need for individual research teams to generate their own stem cell lines and in turn to reduce the use of human tissues and embryos" (UK Stem Cell Bank, 2007). Likewise, the core mandate of the European Human Embryonic Stem Cell Registry (hESCReg) aims for the "responsible limitation of the number of embryos needed for derivation of new cell lines..." (European Commission, 2008).

In this study, we report the preliminary findings of a survey of stem cell banks participating in the International Stem Cell Forum's International Stem Cell Banking Initiative (ISCBI) (Table 1). The questionnaire circulated to all ISCBI members addressed both the general issues surrounding research policies (e.g., national policies regulating the permissibility of conducting embryonic stem cell research (hESCR)) and, more specifically, the issues relating to the governance of stem cell banking projects. The results of the questionnaire were complemented by scholarly research conducted by the authors.

This article provides an overview of the current international hESC banking landscape (I). For this purpose, the policy and governance approaches adopted in the surveyed stem cell banks at the national level will be analyzed and areas of convergence and variance will be identified(II). It is beyond the scope of this paper to provide a comprehensive analysis of the wide range of possible governance approaches, policy responses, and their implications. However, we want to provide a starting point for discussion surrounding key questions and challenges as concerns provenance, access, and deposit of hESC lines (III). Finally, while our analysis is focused on research grade hESCs, the lessons to be gleaned from this examination will encourage further thought, analysis, and research into the issues raised in the banking and governance of other sources of stem cell lines (e.g., SCNT, parthenogenesis, iPs) (IV).

I. International stem cell banking initiatives: Toward harmonization and standardization

The emergence of national stem cell banks is accompanied by the establishment of international initiatives addressing harmonization and standardization processes for stem cell research and banking. These initiatives share the vision of stem cell research as a global enterprise. They are as follows: the International Stem Cell Banking Initiative (ISCBI) by the International Stem Cell Forum, the European Commission's Human Embryonic Stem Cell Registry (hESCReg), UMASS International Stem Cell Registry, and finally, the "Registry of Human Embryonic Stem Cell Lines Provenance" by the International Society for Stem Cell Research (ISSCR).

Table 1 ISCBI registry of national banks/registries of stem cell lines

Canada	• CIHR National ES Cell Registry
United States	• National Stem Cell Bank/ NIH Human Pluripotent Stem Cell Registry
	• Harvard University Human Embryonic Stem (HUES) Cell Collection
	• WiCell International Stem Cell (WISC) Bank
	• UMASS International Stem Cell Registry
France	• Agence de la Biomedicine National Registry for hESC
Germany	• Charité Cell Bank–Berlin-Brandenburg Center for Regenerative Therapies
Israel	• Tel Aviv Sourasky Medical Center Cell Bank
Spain	• National Stem Cell Bank–Banco Nacional de Lineas Celulares (BNLC)
	• Valencia Stem Cell Bank (CIPF)–BNLC Branch
United Kingdom	• UK Stem Cell Bank
European Union	• Human Embryonic Stem Cell Registry (hESCreg)
India	• National Centre for Cell Science (National Repository)
Japan	• Stem Cell Research Center, Institute for Frontier Medical Sciences, Kyoto University
	• RIKEN Bioresource Center–Cell Bank
Korea	• Korean Stem Cell Bank
Singapore	• Singapore Stem Cell Bank
Taiwan	• Taiwan Stem Cell Bank

The above-noted initiatives also share a common goal: the promotion of international collaboration for the timely realization of the scientific promise offered by stem cell research. Thus, they seek policy harmonization along with the standardization of technical standards and safety requirements. They further aim to provide guidance on how to navigate the "policy patchwork" that characterizes the current state of stem cell research.

A description of the international initiatives mentioned requires the clarification of terminology. There is confusion in both the general and the scientific literature[1] regarding the concepts of harmonization and standardization (or unification). We have described elsewhere the nature and scope of these two very distinctive processes and terms (Isasi, 2009).

The term "harmonization" refers to the process in which diverse elements are combined or adapted to each other so as to form a coherent whole, while retaining their individuality (Boodman, 1991). Harmonization is thus a process of recognizing and reconciling differences, which presupposes and preserves the diversity of the objects to be harmonized. In the context of stem cell research, we see policy harmonization in the adoption of a framework of fundamental ethical and governance principles (Isasi and Knoppers, 2006b) (i.e., respect for autonomy, privacy, and confidentiality; ethics review; oversight; etc.) regulating the derivation, use, and banking of hESC lines, albeit with different cultural and local interpretations. Thus, harmonization should be identified with policy convergence as opposed to standardization or unification. In contrast, the term "standardization" refers to the processes of scientific guidance in the adoption of uniform scientific and technical requirements and common guidelines (International Conference on Harmonisation website). Furthermore, the standardization of policies or practices seeks the adoption of uniform model codes, guidelines, or treaties. Consequently, in this article our argument for the adoption of a global governance framework for stem cell banking is a call for policy convergence.

The International Stem Cell Banking Initiative

Despite the proliferation of stem cell banks around the world, a critical discussion about appropriate mechanisms for both domestic and international banking and governance has yet to take central stage. Of particular importance is the challenge of transnational collaboration given the heterogeneity of ethical and legal frameworks affecting the permissibility of conducting stem cell research in all stages, from derivation and use, to banking and distribution.

To address this gap, in 2007 the International Stem Cell Forum launched the International Stem Cell Banking Initiative, with the goal of establishing a set of international minimum standards—or best practice guidelines—for banking, characterization, and testing. It is also the aim of ISCBI to create a solid ethical framework for international cell banking and research.

The International Stem Cell Banking Initiative aims to promote, among other things, minimum standards for cell line quality control and comparability of data produced in different centres around the world. An additional objective is to facilitate the international exchange of cell lines and other research materials. Furthermore, it is the goal of ISCBI to create a global network of stem cell banks by providing support to existing banks and encouraging the development of new banks in member countries. To achieve this objective, the ISCBI has established a Registry of National Banks of Stem Cell Lines.

A key output of the ISCBI has been the adoption of a "Consensus Guidance for Banking and Supply of Human Embryonic Stem Cell Lines for Research Purposes" (ISCF; International Stem Cell Banking Initiative, 2008), which seeks to standardize and establish best practice for the banking, testing, and distribution of hES cells for research purposes. The guidance covers a wide range of processes involved in stem cell banking (e.g., procurement of cell lines, cell banking procedures and documentation, cell banking quality control, and process of releasing cell banks) and establishes technical requirements (e.g., release criteria, microbiological testing, cell characterisation. and shipment of cells). It also addresses core ethical issues (e.g., informed consent, oversight, and licensing; traceability and documentation of cell provenance).

European Human Embryonic Stem Cell Registry

Another important harmonization and standardization effort that highlights the significance of international cooperation is the European Commission's initiative in the creation of a Human Embryonic Stem Cell Registry. The recently launched European Embryonic Stem Cell Registry was founded within the 6th Framework Programme for Research and Technological Development of the *European Commission* (European Parliament, 2002; European Commission, 2006). The hESCReg aims to systematically and comprehensively catalog cell derivation and cultivation methods, gene and protein expression profiles, and available biological data *in vitro* and *in vivo*. It will also examine legal documentation from hESC lines obtained from ongoing and future European Commission-funded research projects.

Following European policy, the registry will not accept stem cell lines that have been created through research that implicates any of the nonfundable activities (European Parliament, 2006) (European Council, 2006), nor will it accept proposals for use of registry cells for any such research. Since research activities destroying human embryos are not eligible for EU funding, stem cells procured through these prohibited research activities are not eligible to be registered. However, it is important to note that research using stem cells derived from surplus human embryos may be eligible for EU funding following the ethical approval required for all EU-funded research (European Embryonic Stem Cell Registry website).

The European hESCReg was created to foster transnational networking between banks and researchers worldwide. It provides both an internet portal to facilitate research projects and ongoing access to comprehensive information about human embryonic stem cell lines. Given the variety of policy approaches regarding stem cell research in Europe, the hESCReg can be seen as a pilot project aiming to solve the

[1] For instance, see the following statement: "although we should not expect harmonization of international laws with respect to stem cell research, we should strive to develop international consensus on ethical and scientific standards and practice…" Matthews, D.J., Donovan, P., Harris J., et al. 2006. Integrity in International Stem Cell Research Collaborations. Science 313, 921-392.

interoperability challenges (i.e., technical, legal, and ethical) arising from transnational collaboration in the field.

UMASS International Stem Cell Registry

Launched in 2008, the International Stem Cell Registry at UMASS was funded by the Massachusetts Life Science Center, with the mission of "providing a searchable, comprehensive database that includes published and validated unpublished information on all of hESC and other pluripotent cell lines (e.g., iPS) (UMASS International Stem Cell Registry website). The registry seeks to be comprehensive in scope and so will accept stem cell lines derived by or deposited in national and international stem cell banks, industry, academic centers, and nonprofit institutions. Furthermore, information about the provenance of the lines is also collected by the registry as well as scientific literature relating to the stem cell lines (Luong et al., 2008). If successful, the registry will provide a major contribution to the field, as it has been designed to be a one-stop shop repository of comprehensive, public, and current information regarding pluripotent stem cell lines worldwide.

International Society for Stem Cell Research (ISSCR)—"Registry of Human Embryonic Stem Cell Lines Provenance"

The International Society for Stem Cell Research is another initiative to foster global governance and facilitate international cooperation in stem cell research and banking. ISSCR seeks the harmonization of core ethical principles through the adoption of the "Guidelines for the Conduct of Human Embryonic Stem Cell Research" (ISSCR, 2006). The guidelines seek to promote responsible, transparent, and uniform practices worldwide.

In the specific context of stem cell banking, the ISSCR's guidelines encourage the establishment of national and international repositories to facilitate the exchange and dissemination of stem cell lines. They also call for the adoption of standardized methods and practices. Furthermore, the guidelines propose the creation of a "Registry of Human Embryonic Stem Cell Lines Provenance." The proposed registry, which will be developed, maintained, and curated by ISSCR, consists of the creation of an online database providing independent validation of the provenance of human embryonic stem cell lines. The registry is still under development and no information has been disclosed regarding its governance structures and operating procedures for documentation and evaluation, among other important issues. Consequently, questions remain as to how ISSCR will deal with issues such as quality control, validation, accountability, and liability given its lofty goal of providing a certificate of "validation" vouching for the ethical and legal provenance of the registered stem cell lines.

II. National approaches to hESC banking

As noted in the Introduction, the present study aims to provide an overview of the current hES cell banking landscape (see Table 1). The analysis that follows is based on a review of the 18 institutions (13 jurisdictions) that participated in the ISCBI survey. The information collected was obtained by direct responses to the survey and complemented by information available in public sources. It should be noted that the majority of these banking initiatives are still under development. It should also be noted that as the field is rapidly evolving our findings reflect the state of activities as of March 2009.

In the spirit of international and public transparency one could presume that the governance structures and processes adopted by stem cell banks and registries would be made available for evaluation and quality control by anyone seeking to use or study them. However, this was not the case for a number of stem cell banks and registries. The lack of disclosure of information is an ethical issue in itself that deserves further analysis in the future.

The first convergent point in the banks under study relates to their objectives: they all aim to avoid redundancy in research projects and to eliminate the need for derivation of additional stem cell lines (e.g., UK, Canada, and Spain). A second point is that the banks largely aim to guarantee the quality, availability, and ethical provenance of the hESC lines they curate (e.g., UMASS, European hECReg). With respect to their role in quality and safety assurance, their mandate includes the characterization, culture, and maintenance of the cell lines. Additionally, the provision of technical support to the research community constitutes one of their core objectives. In summary, such stem cell banks have been created with the lofty goal of being the stewards of the scientific (and ethical) integrity of the stem cell lines they acquire, store, and distribute (e.g., UK, India, Singapore, Korea, Spain).

Nevertheless, divergence is also present in the approaches that countries and jurisdictions have taken to create and govern stem cell banks and registries. Some stem cell banks and registries have been statutorily created (e.g., legislation or executive orders), their mandate and governance structure established through specific legislation (e.g., Spanish National Stem Cell Bank, UMASS). In some cases, the enabling act that created and empowered the bank is primary interpreted by the institution itself (Huhn, 2002). The Spanish National Cell Bank is a clear example of this public ordering approach, as the bank's mandate and structure is confined to the enabling legislation (Spain, 2007). Others are regulated by the rules governing biobanks generally (e.g., Japan, Korea, and Singapore). Finally, some banks and registries have opted for a private ordering approach through self-regulation in their creation and governance structure, and so they lack a legally binding structure (e.g., UK Stem Cell Bank, Singapore, and Israel).

All current banking initiatives foresee, like the immortal cell lines they curate, a long-term existence. In fact, in most cases a platform is created for prospective banking, research, and clinical applications, and for collection, storage, and research uses on an ongoing basis (UK, WiCell, UMASS, European hESCReg, and Spain). Notwithstanding, provisions pertaining to the eventual closure or transfer of assets of the institution, including measures relating to the consequent disposition of the stored samples and data, are sorely lacking in most of the cases under study. Similarly lacking are provisions relating to liability issues. This vacuum has the potential concomitant effect of weakening procedures intended to provide the institution with an accountable and transparent governance framework.

III. Provenance, access, and deposit of hESC lines

Reflecting the national policy frameworks governing the permissibility of conducting stem cell research in their respective jurisdictions, stem cell banks have adopted different criteria with regard to the cell lines that can be deposited in their facilities. For instance, in both the British and the Spanish national banks, cell lines of both embryonic and adult origin are to be deposited. Whereas in the United States, deposit in the National Stem Cell Bank is restricted to only those hESC lines that are eligible for federal funding. Likewise, the French registry accepts for deposit hESC lines derived or used in the country.

In many cases, licensing and funding requirements legally bind researchers to deposit any resultant stem cell lines (and accompanying data) in the bank or the registry (e.g., Spain, UK, European hESCReg, France, Japan, and India). The purpose of this requirement is twofold: first, to ensure tight regulation and appropriate governance, and second, to ensure effective pooling of resources among the scientific community (e.g., France, Japan, Singapore, Thailand, Korea, Czech Republic, Australia (to be established) and Canada (to be established)).

Moreover, the mechanisms for deposit and access vary greatly across the banks. In the UK, for instance, applications for deposit and access (UK Stem Cell Bank, 2007) to the stem cell lines are subject to approval on a case-by-case basis by a nonstatutory body, the *Steering Committee for the UK Stem Cell Bank and for the Use of Stem Cell Lines*. The criteria adopted by the Steering Committee reflect the principles adopted in HFEA's policy. It states that the lines "have been ethically sourced, with fully informed donor consent, and that the cell lines present a valuable resource for the biomedical research community" (UK Stem Cell Bank, 2007). Overall, the Steering Committee ensures that cell lines are used only by bona fide research groups for justifiable and valuable purposes that reflect the requirements of the HFEA regulations.

As is the case of other national stem cell banking initiatives, the UKSCB receives cell lines from elsewhere but mandates deposit by its licensing authority. The UKSCB is the regulator-mandated repository for all embryonic stem cell lines derived in the UK. The *Human Fertilisation and Embryology Authority (HFEA)* requires as a condition for the licensing of newly derived hESC lines that a sample line be deposited in the UK Stem Cell Bank. Likewise, in Spain and France it is statutorily mandated that all stem cell lines created with either private or public funds in the country must be deposited in the respective national banks. Similarly, in the United States all pluripotent cell lines derived using federal funds (NIH, 2007) must be deposited in its National Stem Cell Bank.

In Spain, access to stem cell lines deposited in the bank is on a case-by-case basis and is subject to a license by the *Commission of Guarantees for the Donation and Use of Cells and Human Tissues*, and by the *Autonomous Community Authority*. Requests for access must follow the ethical, legal, and technical requirements established in the law and the bank's regulations (e.g., informed consent, ethics review and approval, and the prohibition of financial gain for the donation of reproductive materials) (Spain, 2006, 2007).

Policy convergence across national stem cell banks is present in the adoption of fundamental ethical principles and research governance requirements across jurisdictions. Specifically, policy convergence is amenable to core ethical principles such as respect of autonomy (e.g., informed consent), respect for privacy and confidentiality (e.g., protection for donor identity given the potential for traceability in hESC lines), and noncommercialization of human reproductive materials (translated in restrictions on monetary compensation for gamete and tissue donation). However, a number of initiatives have no information available with respect to the measures implemented to protect the privacy and confidentiality of donors of reproductive materials (e.g., India, Israel, France, Spain, Japan, Korea, etc.).

Furthermore, in terms of research governance provisions, convergence is also present in the adoption of internal mechanisms for the scientific and ethics review of: (a) the procurement of gametes, embryos, and other cells from human donors for the generation of stem cell lines; and (b) the research and use of already derived hESC lines.

The requirement of demonstrating ethical and scientific provenance of the cell line as a condition of license is the one procedural mechanism with the greatest impact on stem cell research. Such an oversight mechanism, with its traditional requirements of certification, quality assurance, standard operating procedures, reporting procedures, and ethics approval, can effectively frame and even curtail access and thus influence the conduct of research itself. Nonetheless, very little has been said with respect to the type of ethical review and ongoing oversight that is required for long-term infrastructures like stem cell banks and registries.

In terms of ethical and scientific assessment, across the board, all banks require proof of prior local ethical and scientific review and approval, as well as compliance with licensing requirements by the appropriate local entities (e.g., Israel, Japan, UK, Spain, India, UMass, European hESCReg, and WiCell). However, the majority of banks under study have yet to establish transparent and consistent criteria for the accessing and depositing of stem cell lines derived in a foreign jurisdiction (e.g., Harvard University Stem Cell Collection, Japan, India, and Korea).

Likewise, provisions to assess review processes or to verify transnational practices and standards, in order to vouch for the ethical, scientific, and legal provenance of a stem cell line of foreign origin, are only emerging. Given the international realities of stem cell research, this significant gap in existing regulatory frameworks has the potential to constitute a serious roadblock for seamless international collaboration, and ultimately, for the fulfillment of the goals of a stem cell banking initiative in itself. Accordingly, initiatives like the one proposed by ISSCR with the creation of a registry validating the provenance of hESC lines, and the already created European hESCReg and Umass International Stem Cell Registry, have important roles to play in order to fill this vacuum.

In terms of the transnational sharing of stem cell lines in general, three emerging policy options have been proposed or implemented in various jurisdictions (Lomax and McNab, 2008; Isasi, 2009) (Table 2). They consist of policies (a) mandating absolute ethical and legal equivalency (e.g., Czech Republic) or (b) establishing reciprocal policy agreements in order to grant (presumed) ethical provenance of the cell lines (California CIRM, Canada CIHR, and UK SCB). Finally, a common approach is to resort to the use of broad (and sometimes vague) "substantially equivalency" or "acceptably derived" criteria

Table 2 Cross-jurisdictional transfer of hESC lines: Policy approaches [a]

Policy approach	Advantages	Disadvantages and challenges
"Absolute Ethical and Legal Equivalency" Criterion: • Requires absolute ethical and legal equivalency across national policies. • Local laws and regulations are the only acceptable model.	• Mechanisms for assessment and review of practices are clear.	• Confuses policy convergence with unification or standardization. • Ignores sovereignty and moral diversity • Unfeasible and excessively stringent • Restricts availability of hESC lines (e.g., grandfathering clauses not allowed)
"Substantially Equivalent" Criterion: • Derivation, research, and banking are permissible provided that the jurisdictions adopt substantially equivalent ethical and legal requirements.	• Policy convergence toward core socio-ethical concerns and fundamental ethical principles. • Represents a true harmonization process. • Encourages cross-jurisdictional collaboration.	• Potential challenges are to maintain internal consistency when judging the substantial equivalency of policies and to avoid arbitrary applications.
"Reciprocal Policy Agreements" Criterion: • Transnational transfer of cells accepted if hESC lines have been derived by, deposited in, or approved for use by a licensed entity formally recognized as having adopted consistent ethical and legal standards.	• Harmonization effort aimed at avoiding patchworks within jurisdictions by consistently requiring compliance with set ethical and other requirements. • Facilitates research cooperation while respecting divergence in national policy approaches. • Efficient and transparent approach.	• Dangers of internal inconsistencies with respect to national policies.

[a] Excerpts from: Isasi, R.M., April 2009. Policy interoperability in stem cell research: demystifying harmonization. Stem Cell Rev and Rep (2009) 5:108–115.

(e.g., USA NAS, UKSCB).[2] All of these policy approaches—albeit with different degrees—pose challenges in terms of assessing variations in the regulation of core ethical requirements across jurisdictions. A further challenge they pose is the maintenance of internal consistency and transparency with regard to their policy frameworks governing stem cell research in general. For instance, how to determine which variations should be deemed as significant enough as to erode the core ethical principles and moral values enshrined in a given jurisdiction? How to evaluate the context in which derivation, research, and distribution take place? On the other hand, a major advantage of the latter two approaches is that they provide prospective strategies toward streamlining review processes and the verification of cross-jurisdictional practices and standards.

The transnational sharing of stem cell materials and related data are largely dependent on the ability of stem cell banks to harmonize in many crucial areas—not least with regard to normative and ethical principles, oversight, governance mechanisms, technical and security standards, quality assurance, and scientific practices. The absence of provisions addressing the cross-jurisdictional sharing of hESC lines could thwart the advancement of research by potentially limiting some transactions, narrowing then the availability of hESC lines, and consequentially impacting the quality and nature of the research. Accordingly, the adoption of interoperable quality assurance standards and clear consents to international access and exchange are essential.

A flexible and proactive global integration strategy is also imperative for the viability of a stem cell bank. Current heterogeneous socio-ethical and policy frameworks, along with contentious domestic socio-political contexts, pose a great challenge for international cooperation. While domestic and scientific goals are necessarily culturally determined, safety through quality assurance and ongoing research that honors the consent of donors can only be achieved through ensuring some level of interoperability via governance structures.

IV. Governance structures

Governance has been generally defined as "the exercise of authority within a given sphere. It has often been employed as a synonym for the efficient management of a broad range of organizations and activities" (Hewitt, 2002). The sustainability of stem cell banks and registries depends on the implementation of governance mechanisms that ensure their scientific and ethical integrity. In order to achieve this, their governance structure, processes, and bodies must be

[2] The British NSCB, for instance, accepts stem cell lines where ethical sourcing can be presumed, as it is the case for stem cell lines that are registered in the United States National Institute of Health's Pluripotent Stem Cell Registry. It is the mandate of the UKSCB Steering Committee to establish the criteria for ethical provenance.

Table 3 Similarities and differences in the dealing with governance issues

	Convergence	Divergence and gaps
Policy approaches	Internally consistent with general policy frameworks relating to the permissibility of conducting stem cell research.	Mixture of public and private ordering (i.e., statutorily created or self-regulated).
Funding sources	Public funding	Funding sources and their governance differ. They seldom influence the institution's independence, transparency, and accountability.
Mandate and objectives	Often well-defined and coordinated objectives: Main goal is the centralization of quality controlled and ethically sourced hSCL.	Lack of proactive international strategy. However, some institutions adopt a prospective approach and flexible mandate.
Provenance of human stem cell lines (hSCL)	The majority of the institutions accept hSCL of different origins (embryonic, adult) and grades (research and clinical grade).	Some institutions have adopted strict criteria to further limit the kind of hSCL they can receive (e.g., USA NSCB, hESCReg).
Policies for access and deposit of stem cell lines (hSCL)	Mostly transnational scope. Case-by-case approval by the institution's oversight body. Need proof of prior local ethical and scientific review and approval. To ensure tight regulation and effective pooling of resources among the scientific community, in many cases licensing and funding requirements legally bind researchers to deposit hSCL.	Lack of comprehensive and transparent provisions for the transnational transfer of hSCL. Criteria for deposit and access vary greatly across the institutions.
Transnational resource sharing and access	Tend to promote the availability of hSCL and data to the widest audience.	Lack of clear and harmonized guidelines for the scientific and ethical assessment of hSCL derived outside the jurisdiction.
Governance structures	Most institutions adopt a centralized and multilayered structure. Recognition of the need for adequate scientific and ethical oversight All initiatives are of long-term existence: A platform has been created for prospective banking, research and clinical applications, anticipating collection, storage, and research uses on an ongoing basis.	Some governance structures are complex and inflexible and present deficiencies in terms of accountability, transparency, and independence. Lack of clear provisions pertaining to: • Ongoing oversight and enforcement mechanisms. • Closure or transfer of assets, including measures relating to the consequent disposition of stored samples and data. • The avoidance of systemic conflicts of interest. For instance, there is a lack of separation between the organization funding and managing the initiative, as well as in terms of their research and banking platforms.
Governance bodies	Range in their nature: advisory-consultative to executive-statutory. Mostly multilayered and collegiate bodies with limited multidisciplinary membership.	Degrees of independence and accountability of governance bodies vary across the institutions. Multidisciplinary membership not always adopted; favouritism toward "professional expertise." Lack of representation of all stakeholders problematic in terms of maintaining legitimacy.

independent, accountable, and transparent (Cambon-Thomsen et al., 2007).

Good governance should be understood at all levels, from the original institutional design to institutional performance. In addition, governance mechanisms act at two levels: at the internal level through mechanisms governing the day-to-day activities of the bank, and at the external level, by independently assessing the overall bank performance and making the bank accountable to all its stakeholders.

Although the specific scope and governance structure of national stem cell banks and registries vary, they all accord importance to the centralization of quality-controlled and ethically sourced stem cell lines. Likewise, the majority share concerns over governance mechanisms that promote transparency, stewardship, and accountability, as well as generate public support. The process chosen to create, govern, and evaluate the scientific and ethical integrity of the initiative (being the bank or the registry) must also ensure the legitimacy of its "raison d'être" (Deschenes and Salle, 2005).

The UK National Stem Cell Bank thanks to its visionary design is the first to have an infrastructure ready to receive, store, and supply stem cell lines from a variety of technologies (e.g., reprogramming, somatic cell nuclear transfer) and for distinctive purposes (e.g., research and clinical applications) (UK Stem Cell Bank, 2007). The UKSCB governance structure is perhaps the most comprehensive of all existing stem cell banks. Similarly, the Spanish National Stem Cell Bank, the USA National Stem Cell Bank, and the European hESCReg, among others, present clear governance structures. However, the latter is not the case for all the banks under study. In some cases, their governance structures and bodies are not publicly disclosed, and thus, it is difficult to determine their level of transparency and independence (e.g., Harvard University Human Embryonic Stem Cell Collection, India, Japan, Korea, and Singapore).

It could be argued that the governance structures established for stem cell banks should adopt a prospective approach. Establishing a flexible and organic infrastructure mindful of future needs and international norms could accommodate the rapidly evolving nature of the stem cell research field. The design of some stem cell banks as noted above (e.g., UK, UMass, Singapore) reflects this need. Since their inception they have been conceived as repositories of stem cell lines of different origins (e.g., somatic and embryonic), grades (research and clinical), and sources (local or transnational). Conversely, other initiatives (e.g., Spain)—for political reasons—have opted for a rigid approach by limiting the breadth of lines they curate, thus not taking into account the rapidly evolving nature of scientific developments. To accommodate the latter, the creation of additional infrastructures and governance frameworks would be needed.

Common to the majority of institutions under study is public funding (e.g., UK, Spain, USA NSCB, France, European hESCReg, UMass, and Singapore). However, it is not clear from the information available what influence—if any—the funding sources and their mechanisms of distribution play in terms of the institution's independence, transparency, and accountability. Good governance practice calls for a separation between the organization funding and managing the initiative, from that conducting the review and ongoing oversight. Multilayered governance configurations are necessary to promote independence, objectivity, and transparency.

Likewise, it is not clear if in all the institutions studied, their governance bodies (especially those in charge of granting licenses for access to, and deposit of, stem cell lines) are independent from their internal governance structures or from the management of the institution. This independence provides a needed additional system of checks and balances as well as accountability (e.g., Spain). Furthermore, the separation between governance bodies is desirable in order to safeguard the interests of the banks' wide range of stakeholders and to ensure good ethical practice. Independence is necessary to avoid the risk of these institutions ending up as being self-serving or being perceived as such.

Similarly, not all institutions maintain independence between the banking and the research platforms (e.g., Spain, Singapore). Such a separation is much needed in order to maintain a balance between public interests and that of third parties, including the research community, as well as to avoid systemic conflicts of interest. The only exception to this is the UKSCB, as its Code of Conduct explicitly preempts the bank from conducting research that might be seen to produce a conflict of interest between its core mandates, the distribution of quality stem cell lines and the free dissemination of accompanying information.

Governance bodies adopted in the banks under consideration range in their nature: from advisory-consultative to executive-statutory. Similarly across the board, the powers, roles, and responsibilities of governance bodies tend to vary quite markedly. Mechanisms for oversight and accountability have been integrated in different ways, some of them within the same structure of the organization (e.g., UK), while others imposed through legislation (e.g., Spain) or the result of a contract or licensing agreement (e.g., USA NSCB, European hESCReg).

Transparency on the powers and the composition of oversight bodies is a sine qua non requirement for sound governance. However, in most of the institutions under study, there is lack of transparency in terms of which of the governance bodies—if any—has the authority to impose sanctions for violation of policies and legal norms, or for the ongoing oversight of specific research projects once the stem cell lines have been released to external users.

Additionally, with regard to the composition of these governance bodies, of key importance is the issue of multidisciplinary membership in order to reflect the multiplicity of interests at stake, and hence to maintain legitimacy. It is not apparent whether in the institutions under study membership is restricted to professionals or experts, leaving aside, for example, the lay public as it is the case with the Spanish National Stem Cell Bank, the European hESCReg, and the US National Stem Cell Bank.

Conclusion

Certain issues and challenges dominate the stem cell banking landscape explored here. While it is recognized that "stem cell research is a global enterprise that begins at the local level" (O'Rourke et al., 2008), the majority of current and emerging national stem cell banking initiatives are not adopting a global and prospective strategy. What is of heightened concern is the fact that despite these platforms being built with the goal of maximizing the reproducibility, comparability, and transparency of the field (European Group of Ethics in Science and New Technology, 2007), they often lack a comprehensive and transparent ethical and governance framework (Table 3).

In this study, we have identified central issues, convergence points, and gaps in the adoption of such framework, as well as demonstrated the increasing need for the adoption of

both domestic and international policies providing ethical and scientific guidance.

Yet, several international initiatives seeking harmonization of policies and standardization of scientific practices are emerging (e.g., ISSCR, ISCF, UMass). They all seek global leadership so as to complement the role of national stem cell banks. What is more, giving the proliferation of national banks, these international initiatives aim to achieve the very important goal of interconnecting national efforts in order to facilitate international collaboration. Whether these transnational attempts will succeed, or whether a global governance framework will emerge from them, remains to be seen.

A major challenge arising is that the proliferation of both national and international stem cell banks is creating a complex patchwork, with institutions competing and duplicating objectives and mandates. The latter is further complicated by disjointed plans for collaboration between institutions. As it becomes evident, these shortcomings are not only creating inefficiencies in terms of the use of resources and the facilitation of access but most importantly, they are defeating the original objective that supported the creation of these institutions in the first place. All of these banks were created with the shared objectives of fostering and streamlining international collaboration and the sharing of data and materials, avoiding redundancy in research projects and eliminating the need for the derivation of additional stem cell lines. To achieve maximal effectiveness what is needed is a global approach that builds collaboration among all institutions (Luong et al., 2008).

Most important are the issues of legitimacy and transparency. Public trust is essential for the feasibility of any scientific endeavor but even more so in an area that has elucidated so much political, social, and ethical controversy, that of embryonic stem cell research. The maintenance of public support is of paramount importance to ensure the legitimacy of the banks. Trust is in great part influenced by the effectiveness of the institution's governance structure, the strength of monitoring, and of scientific and ethical oversight and by the mechanisms ensuring transparency, independence, and accountability. It is thus problematic that —at least for those initiatives already in operation—there is not public disclosure of their governance structures and their procedures for sourcing and validation (both scientific and ethical) of the hESC lines they curate.

Finally, while beyond the scope of the present study, it should be noted that the majority of the institutions reviewed, despite being publicly funded initiatives, have yet to address the challenges posed by social justice issues related to equitable beneficence (Faden et al., 2003) in terms of access to research and eventual therapies. Indeed, the creation of stem cell banks raises fundamental issues of distributive justice and reciprocity for participating individuals and populations that must be taken seriously.

Acknowledgments

We thank the Canadian Stem Cell Network, the Canadian Institutes of Health Research, and the International Stem Cell Forum for their funding support. Our funding sources have played no role in the design, interpretation, and writing of the present study. The authors are especially grateful to Michael Le Huynh for providing expert research assistance and valuable comments, the members of the International Stem Cell Banking Initiative, and the anonymous reviewers, for their comments and thoughtful suggestions on an earlier version of the present article. The opinions are those of the authors alone.

References

Boodman, M., 1991. The myth of harmonization of laws. Am. J. Contemporary Law 39, 699–724.

Cambon-Thomsen, A., Rial-Sebbag, E., Knoppers, B.M., 2007. Trends in ethical and legal frameworks for the use of human biobanks. Eur. Resp. J. 30, 373–382.

Deschenes, M., Salle, C., Spring 2005. Accountability in population biobanking: comparative approaches. JLME 41.

European Commission, January 2008. 6th Framework Programme of the European Commission, Priority 1.1.1, Life Sciences, Genomics and Biotechnology for Human Health. European Human Embryonic Stem Cell Registry—EU hESC registry. http://www.stemcell.no/pdf/EU%20HESC%20Registry.pdf.

European Parliament and European Council, June 2002. Decision No. 1513/2002/EC, concerning the sixth framework programme of the European Community for research, technological development and demonstration activities, contributing to the creation of the European Research Area and to innovation (2002 to 2006).

European Parliament and European Council, December 18 2006. Decision No. 1982/2006/EC, concerning the seventh framework programme of the European Community for research, technological development and demonstration activities (2007–2013).

European Council, December 2006. Decision No. 2006/971/EC 19 concerning the specific propgramme Cooperation implementing the Seventh Framework Programme of the European Community for research, technological development and demonstration activities (2007 to 2013).

European Commission, December 2006. Statement re. Article 6 for the 7th Framework Programme. European Commission, Brussels.

European Group of Ethics in Science and New Technologies to the European Commission, 2007. Recommendations on the Ethical Review of HESC FP7 research projects, Opinion No. 22. European Group of Ethics in Science and New Technologies to the European Commission, Brussels.

European Embryonic Stem Cell Registry website—FAQs. http://www.hescreg.eu/index.php?pos0=50&pos1=51&MEN=2007-05-30+14%3a27%3a20%23FAQs&lay=3.

Faden, R.R., Dawson, L., Bateman-House, A.S., et al., Nov.-Dec. 2003. Public stem cell banks: considerations of justice in stem cell research and therapy. Hastings Cent Rep. 33 (6), 13–27.

Hewitt, C., 2002. Uses and abuses of the concept of governance. Intl. Social Sci. J. 50 (155), 105.

Huhn, W., 2002. Three legal frameworks for regulating genetic technology. J. Contemp. Health Law Policy 19 (1), 1–36.

Isasi, R.M., 2009. Policy Interoperability in stem cell research: demystifying harmonization. Stem Cell Rev. Rep. 5, 108–115.

Isasi, R.M., Knoppers, B.M., 2006a. Mind the gap: policy approaches to embryonic stem cell and cloning research in 50 countries. Eur. J. Health Law 13 (1), 9–25.

Isasi, R.M., Knoppers, B.M., 2006b. Beyond the permissibility of embryonic and stem cell research: substantive requirements and procedural safeguards. Hum. Reprod. 21 (10), 2474–2481.

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. www.ich.org.

International Stem Cell Forum—International Stem Cell Banking Initiative, http://www.stemcellforum.org/forum_initiatives/international_stem_cell_banking_initiative.cfm.

International Stem Cell Banking Initiative, Registry of National Banks of Stem Cell Lines, http://www.stemcellforum.org/forum_initiatives/international_stem_cell_banking_initiative/registry_of_national_banks_of_stem_cell_lines.cfm.

ISCF International Cell Banking Initiative, February 2008. Consensus Guidance for Banking and Supply of Human Embryonic Stem Cell Lines for Research Purposes. http://www.stemcellforum.org/forum_initiatives/international_stem_cell_banking_initiative/iscbi_guidance.cfm.

International Society for Stem Cell Research (ISSCR), 2006. Guidelines for the Conduct of Human Embryonic Stem Cell Research. International Society for Stem Cell Research, Philadelphia.

Lomax, G., McNab, A., 2008. Harmonizing standards and coding for hESC research. Cell Stem Cell 2, 201–202.

Luong, M.X., Smith, K.P, Stein, G.S., 2008. Human embryonic stem cell registries: value, challenges and opportunities. J. Cell. Biochem. 105, 625–632.

National Institutes of Health, 2007. Plan for Implementation of Executive Order 13435: Expanding Approved Stem Cell Lines in Ethically Responsible Ways. National Institutes of Health, Department of Health and Human Services, MD.

Organization for Economic Co-Operation and Development (OECD), 2006. Creation and Governance of Human Genetic Research Databases. Organization for Economic Co-Operating and Development, Paris.

O'Rourke, P.P., Abelman, M., Hefferman, K.G., April 2, 2008. Centralized banks for human embryonic stem cells: a worthwile challenge. Cell Stem Cell 312.

Spain, July 2007. Law on Biomedical Research No. 14.

Spain, 8 February 2006. Order SCO/393/2006 by which organization and functioning of the National Cell Line Bank is established.

Stacey, G.N., 2007. Sourcing human embryonic stem cell lines. In: Sullivan, S., Cowan, C.A., Eggan, K. (Eds.), Human Embryonic Stem Cells: The Practical Handbook. Wiley, Chichester.

UK Stem Cell Bank, January 2007. Code of Practice for the Use of Human Stem Cell Lines. Stem Cell Steering Committee, London.

UMASS International Stem Cell Registry, http://www.umassmed.edu/iscr/index.aspx.